Diisocyanates Panel

Scientific Information Statement with References

Urine Biomonitoring for MDI Exposure

1. Introduction

Methylene diphenyl diisocyanate (MDI) is a chemical compound that reacts rapidly with polyols and amines to produce rigid polyurethane foam and is also used as a binder for adhesives and wood products. MDI has been well studied and safety precautions and engineering controls are available to help protect workers and the public.* Worker exposure to MDI usually is evaluated by ambient air monitoring. Occasionally, biological monitoring has been used. The American Conference of Governmental Industrial Hygienists (ACGIH) has established a threshold limit value (TLV) for worker exposure to MDI in workplace air.

MDI has been seen to cause allergic sensitization responses in guinea pigs.[1,2] In addition, persons exposed to high levels of MDI may become sensitized and may experience adverse pulmonary symptoms on re-exposure to MDI at levels below the exposure limit.[3] To prevent pulmonary effects and sensitization in workers potentially exposed to MDI, ACGIH has established a TLV of 0.005 ppm (time weighted average).[4] Air concentrations of MDI in the workplace have been shown to be generally less than 0.001 ppm, indicating low exposure potential via inhalation.[5,6,7]

Three large studies of cancer incidence or mortality have been conducted in the polyurethane foam industry, which primarily involved the use of toluene diisocyanate.[8,9,10,11] These studies do not show a consistent relationship between cancer incidence and diisocyanate exposure.[12] In rats exposed to polymeric MDI† aerosol at 0, 0.19, 0.98, 6.03 mg/m^3 in a two-year study, changes in the respiratory tract included pulmonary adenomas (six rats) and one adenocarcinoma in association with other inflammatory changes, suggesting that the tumors were a result of recurrent injury.[13] Mixed results have been obtained with genotoxicity assays, possibly due to the instability of MDI in water. These *in vivo* genotoxicity studies may be unsuitable for risk assessment, though additional research is ongoing to evaluate a report indicating increased micronuclei formation followed high level exposure of rats to MDI aerosol.[14] The U.S. EPA has classified MDI and polymeric MDI as Group D – not classifiable as to carcinogenicity.[15] The International Agency for Research on Cancer (IARC) also has determined that MDI is not classifiable as to carcinogenicity in humans (Group 3), noting the limited evidence in experimental animals.[16]

2. MDI Exposure Assessment as Hydrolyzed Methylene Dianiline in Urine Samples

A number of air monitoring methods have been developed to determine ambient concentrations of MDI in workplace air. With appropriate expertise and equipment, the measurement of exposure to MDI can be performed with a high degree of accuracy.[17] In addition, biological monitoring for MDI has been suggested and occasionally used to address

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* Material Safety Data Sheets, available from MDI suppliers, provide additional health and safety information regarding this chemical.

† Polymeric MDI contains approximately 50 % MDI and 50 % oligomers (chains of several MDI molecules reacted together).

workplace scenarios where individuals are involved in different processes, with large variation of exposure levels. Sophisticated analytical methods are used to estimate, in urine samples of MDI-exposed individuals, the total amount of the chemical that might have been inhaled or absorbed during a work shift. The advantage of this approach is that, in principle, the "total dose" for an individual may be estimated. However, due to inter-individual variation in metabolism and pharmacokinetics, such biological monitoring data may vary greatly and, therefore, may not be sufficient to accurately determine exposure to MDI.

2.1 Methodology

Biomonitoring assays estimate total MDI exposure by converting MDI and its urinary metabolites to methylene dianiline (MDA) by acid or base hydrolysis. The estimation of MDA in hydrolysed samples is used as a measure of total MDI metabolites in the urine. Skarping *et al.* first investigated and described biomonitoring of MDI-exposed workers in 1994.[18] Other research groups have published different analytical methods. Virtually all of these methods use the same principle of collecting urine samples, and applying vigorous acid hydrolysis prior to chromatography analysis to measure total MDI exposure.[5,18,19] Historically, sampling has been done at single time points or at collection intervals up to 114 hours post exposure.[20] A variety of analytical methods (e.g., chromatography) are used to determine the amount of MDA generated in the laboratory by hydrolysis.[5,18,19] This analytical protocol does not, however, provide information on the relative contribution of any "free" (unconjugated) MDA to total hydrolyzable MDA.[6] Free MDA and the known metabolite, 4-acetyl-MDA, can be quantified by omitting the vigorous hydrolysis step described above.[5]

2.2 Interpretation

Data generated by such urine biomonitoring assays must be evaluated with caution for the following reasons:

1. Data on the metabolic fate in humans of absorbed MDI is incomplete. Metabolites of MDI, measured as MDA, have been found in the urine of workers potentially exposed to MDI.[5,18] However, data are not available in the peer-reviewed literature on the amount of conversion of absorbed MDI to MDA-containing metabolites. In addition, no controlled studies have been performed to determine the amount of MDI absorbed following inhalation or dermal exposure in humans. The magnitude of uptake following inhalation exposure has been determined for the related compound toluene diisocyanate (TDI).[21] The dermal penetration of MDA itself has also been measured in human volunteers.[22] However, since both TDI and MDA have substantially different toxicokinetic profiles than MDI,[23] the uptake data from these two compounds cannot be used to reliably predict dermal or inhalation absorption of MDI. Therefore, derivation of a quantitative estimation of exposure to MDI using hydrolyzed urinary MDA levels is considered premature. A study of the metabolism of MDI in rats is currently being performed; data from that study may assist in addressing this issue in the future.

2. Biomonitoring may provide information on relative <u>cumulative</u> MDI exposure and uptake into the body. However, <u>peak</u> exposures, which may occur over relatively short periods, are believed to be critical in the development of airway sensitization.[3] Because the elimination half-life of MDI metabolites in the urine is 59-82 hours,[20,23] the current biomonitoring methods based on hydrolysis of MDI and its urinary metabolites to MDA provide information on cumulative exposure over the past 2.5 to 3.5 days, but do not indicate whether any peak

exposures may have occurred in that period. Therefore, MDI biomonitoring may not be very useful to evaluate risk of respiratory sensitization and even may be misleading.

3. No data have been generated to show that the acid hydrolysis used in the measurement of "total" MDA affords complete cleavage of the conjugates of MDI and/or MDA present in urine. Skarping *et al.* were unable to achieve complete cleavage of the acid-labile conjugates of TDI present in urine, even after 240 hr.[24] Incomplete cleavage of the metabolites of MDI could result in erroneous total MDA levels.

3. Conclusion

Bioassays have been developed and described to estimate MDI exposure by converting MDI and its urinary metabolites to MDA by vigorous acid hydrolysis, and measuring the hydrolyzed MDA in the urine. Theoretically, this may integrate exposure by inhalation and dermal routes, and would reflect MDI exposure. However, biomonitoring data must be evaluated with caution. The quantitative relationship between exposure and urine levels is not well defined. The detection of MDA in urine samples after vigorous hydrolysis does not reflect the level of free MDA in the body, rather it estimates the combination of conjugated MDI derivatives and free MDA. In addition, application of this methodology may only reflect average daily exposure. Short-term peak exposures, which are considered to be critical with respect to sensitization, cannot be detected via these methods. Based on current methods, urine biomonitoring for MDA conjugates may provide some qualitative guidance for housekeeping and hygiene, but should not be used as evidence for an increased risk of health effects from MDI exposure.

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